Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

SARS-CoV-2 Infection in the Gastrointestinal Tract: Fecal–Oral Route of Transmission for COVID-19?

See "The gastrointestinal tract is an alternative route for SARS-CoV-2 infection in a nonhuman primate model," by Jiao L, Li H, Xu J, et al, on page 000.

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] has devastated the global community. The virus spreads with ease causing multisystemic diseases with a high mortality. Although patients with COVID-19 manifest mainly respiratory diseases, a significant proportion of the patients also developed gastrointestinal (GI) symptoms such as abdominal pain, vomiting, nausea, anorexia, and diarrhea.[2] Accumulating evidence suggests that SARS-CoV-2 infects human via the GI tract,[3] although the underlying mechanism of SARS-CoV-2 pathogenesis in the GI tract and route of infection beyond aerosol transmission are poorly understood. In the current issue of *Gastroenterology*, Jiao et al[4] report evidence for direct GI infection by SARS-CoV-2 and associated GI and systemic pathology in the rhesus macaque model.

Intranasal or Intragastric Inoculation of SARS-CoV-2 Induced Infection and Pathology in Both Respiratory and GI Tissues

In the 5 rhesus macaques intranasally inoculated with SARS-CoV-2, the authors observed histopathologic lesions in both the respiratory and GI tissues. The histopathologic damage in GI tissues includes inflammatory cell infiltrations and mucosal epithelium exfoliation, although the infected animals had no diarrhea. SARS-CoV-2 RNA was detected both in respiratory and GI tissues, and the virus in the GI samples was infectious. In patients with COVID-19, respiratory symptoms may not be the initial presenting symptom; in some cases, diarrhea and fever manifested before respiratory symptoms.[5] Therefore, it will be important to determine how the virus reaches the GI tissues after intranasal exposure, and what factors influence the development of disease within the GI and respiratory systems. In the 5 animals intragastrically inoculated with SARS-CoV-2, viral RNA was detected in GI tissues and contents, as well as pulmonary, pancreatic, and hepatic tissues. The detected virus in these tissues was infectious. Intragastric inoculation with SARS-CoV-2 also caused respiratory dysfunction, as nodular pulmonary infiltrations, as well as gross and histologic lesions in the lung were observed. Surprisingly, viral RNA was not detected in the lung tissue, suggesting that lung tissue damage may not be caused by direct virus replication after intragastric inoculation.

Mechanism of GI Tract Injury Via Direct Virus Replication or Inflammatory Cytokines?

Both bat and human intestinal organoids support robust SARS-CoV-2 replication,[6] and SARS-CoV-2 also productively infects human gut enterocytes.[7] In this study, the authors showed that SARS-CoV-2 infects Caco-2 human intestinal epithelial cells, and that SARS-CoV-2 RNA was detected in GI tissues. Furthermore, the number of mucin-containing goblet cells in GI tissues decreased after both intragastric and intranasal virus inoculation, suggesting dysfunction of the host defense mucus barrier via goblet cell damage. Therefore, it is plausible that the GI damage in patients with COVID-19 is the result of direct virus attack within the GI tract via viral replication in intestinal epithelial cells. In contrast, the authors found that inflammatory cytokines induced by SARS-CoV-2 are the common link in both respiratory and GI tracts, regardless of the route of infection. In animals intranasally inoculated with SARS-CoV-2, 10 cytokines in respiratory tissues and 21 cytokines in GI tissues were up-regulated, suggesting that GI tissue damage may be caused by inflammatory cytokines released from SARS-CoV-2–activated macrophages after intranasal inoculation. Similarly, inflammatory cytokines were also induced after intragastric inoculation, suggesting that the lung damage is mediated via inflammatory cytokines. Additionally, the macrophage marker CD68 expression is increased in GI tissues of intragastrically infected animals, which is consistent with increased inflammatory cytokine levels. In addition, a cytokine storm induced by SARS-CoV-2 has been implicated as the cause of pneumonia.[8,9] The fact that the animals infected by intragastric inoculation in this study had no detectable viral RNA in the lung tissues, but yet exhibited lung damage, lends further credence to a model of cytokine-mediated pathogenesis.

Fecal–Oral Route of Transmission for COVID-19?

Because respiratory symptoms are the predominant clinical manifestation of SARS-CoV-2 infection, aerosol transmission is the major route of transmission in humans. However, the results from this study suggest that fecal–oral route could also be a potential transmission route, because direct GI inoculation resulted in infection and infectious virus could be detected in the GI tissues and content of infected animals. Approximately 48% of patients with COVID-19 in Hong Kong had detectable SARS-CoV-2

EDI 5.6.0 DTD ■ YGAST64031_proof ■ 6 March 2021 ■ 2:09 pm ■ ce

Table 1. GI Diseases Associated with Infection of Representative Coronaviruses

Virus	Genus	Clinical Symptoms and GI Involvement
Transmissible gastroenteritis virus of Swine (TGEV)	*Alphacoronavirus*	Gastroenteritis
Porcine epidemic diarrhea virus (PEDV)	*Alphacoronavirus*	Gastroenteritis
Severe acute diarrhea syndrome-coronavirus (SADSCoV) or swine enteric alphacoronavirus (SeACoV)	*Alphacoronavirus*	Gastroenteritis
Canine coronavirus I (CCoV-I)	*Alphacoronavirus*	Mild enteritis
Canine coronavirus II (CCoV-II)	*Alphacoronavirus*	Mild enteritis, systemic disease
Feline coronavirus I (FCoV-I)	*Alphacoronavirus*	Mild enteritis, asymptomatic infection (FECV), infectious peritonitis (FIPV)
Mink coronavirus (MCV)	*Alphacoronavirus*	Epizootic catarrhal gastroenteritis
SARS-CoV-2	*Betacoronavirus*	Mainly severe respiratory disease; also neurological and GI symptoms (vomiting, nausea, anorexia, and diarrhea)
SARS-CoV-1	*Betacoronavirus*	Mainly severe respiratory disease; also diarrhea (less common and severe than SARS-CoV-2)
MERS-CoV	*Betacoronavirus*	Mainly severe respiratory disease; also diarrhea and vomiting (less common and severe than SARS-CoV-2)
Porcine hemagglutinating encephalomyelitis virus (PHEV)	*Betacoronavirus*	Neurological and/or enteric disease
Bovine coronavirus (BCoV)	*Betacoronavirus*	Calf diarrhea, winter dysentery, and/or respiratory disease
Turkey coronavirus (TCoV)	*Gammacoronavirus*	Enteric diseases
Porcine Delta-Coronavirus (PDCoV)	*Deltacoronavirus*	Gastroenteritis

GI, gastrointestinal.

RNA in stool samples, even after negative tests of respiratory samples.[10] In some patients, viral titers in feces were higher and persisted longer than in respiratory tissues or secretions.[11,12] The average duration for positive respiratory samples is 16.7 days, and for positive stool samples is 27.9 days.[11] Viable SARS-CoV-2 was also detected in other samples from patients with COVID-19 including saliva, urine, and stool.[13] Of note, infectious SARS-CoV-2 was isolated from stool of a deceased patient with COVID-19.[14] In the current study, infectious virus was also re-isolated from a fecal sample of an infected rhesus monkey (MM-O-7). Collectively, the available evidence suggests an alternate fecal–oral route of transmission for COVID-19. Whether the amount of excreted virus in stool could lead to contamination of drinking water or food, especially in developing countries with poor sanitation conditions, warrants further investigation. A recent study supports a fecal aerosol route of transmission.[15] SARS-CoV-2 RNA has also been detected in wastewater or sewage, which could be used for infection surveillance in a given population.[16]

It is not surprising that SARS-CoV-2 can infect via the GI tract, as many other coronaviruses, including some *Betacoronaviruses*, are known to cause GI symptoms (Table 1).[17] The receptor of SARS-CoV-2, *angiotensin-converting enzyme 2*, is abundantly expressed in pulmonary tissues, but is also highly expressed in the GI tissues.[18] Several enteric *Alphacoronaviruses* use a different receptor, the amino-peptidase N, for GI infection, and are mainly associated with GI symptoms.[19,20] Developing a natural animal model that can recapitulate the systemic diseases associated with SARS-CoV-2 infection will be important, because the rhesus macaque, *angiotensin-converting enzyme 2* transgenic mouse, or other animal models do not fully capture the complex natural disease course of SARS-CoV-2 infection in humans. The relatively small number of rhesus macaques used here is also a limitation of the study, but these results should stimulate further in-depth investigation on many important questions regarding GI involvement with COVID-19.

XIANG-JIN MENG Q4
Center for Emerging, Zoonotic and Arthropod-borne Pathogens
Virginia Polytechnic Institute and State University
Blacksburg, Virginia

T. JAKE LIANG
Liver Diseases Branch
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

References

1. Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579:265–269.
2. Chen A, Agarwal A, Ravindran N, et al. Are gastrointestinal symptoms specific for coronavirus 2019 infection? A prospective case-control study from the United States. Gastroenterology 2020;159:1161–1163 e2.
3. Zhong P, Xu J, Yang D, et al. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. Signal Transduct Target Ther 2020; 5:256.
4. Jiao L, Li H, Xu J, et al. The gastrointestinal tract is an alternative route for SARS-CoV-2 infection in a nonhuman primate model. Gastroenterology 2020;160: 00–00.
5. Han C, Duan C, Zhang S, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. Am J Gastroenterol 2020;115:916–923.
6. Zhou J, Li C, Liu X, et al. Infection of bat and human intestinal organoids by SARS-CoV-2. Nat Med 2020; 26:1077–1083.
7. Lamers MM, Beumer J, van der Vaart J, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369:50–54.
8. Buszko M, Park JH, Verthelyi D, et al. The dynamic changes in cytokine responses in COVID-19: a snapshot of the current state of knowledge. Nat Immunol 2020; 21:1146–1151.
9. Nienhold R, Ciani Y, Koelzer VH, et al. Two distinct immunopathological profiles in autopsy lungs of COVID-19. Nat Commun 2020;11:5086.
10. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology 2020; 159:81–95.
11. Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 2020;5:434–435.
12. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. BMJ 2020;369:m1443.
13. Jeong HW, Kim SM, Kim HS, et al. Viable SARS-CoV-2 in various specimens from COVID-19 patients. Clin Microbiol Infect 2020;26:1520–1524.
14. Xiao F, Sun J, Xu Y, et al. Infectious SARS-CoV-2 in feces of patient with severe COVID-19. Emerg Infect Dis 2020;26:1920–1922.
15. Kang M, Wei J, Yuan J, et al. Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. Ann Intern Med 2020;173:974–980.
16. Peccia J, Zulli A, Brackney DE, et al. Measurement of SARS-CoV-2 RNA in wastewater tracks community infection dynamics. Nat Biotechnol 2020;38:1164–1167.
17. Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): a lesson from animal coronaviruses. Vet Microbiol 2020;244:108693.
18. Pirola CJ, Sookoian S. COVID-19 and ACE2 in the liver and gastrointestinal tract: putative biological explanations of sexual dimorphism. Gastroenterology 2020; 159:1620–1621.
19. Li W, Hulswit RJG, Kenney SP, et al. Broad receptor engagement of an emerging global coronavirus may potentiate its diverse cross-species transmissibility. Proc Natl Acad Sci U S A 2018;115:E5135–E5143.
20. Huang YW, Dickerman AW, Pineyro P, et al. Origin, evolution, and genotyping of emergent porcine epidemic diarrhea virus strains in the United States. mBio 2013;4: e00737–13.

Correspondence
Address correspondence to: Xiang-Jin Meng, Center for Emerging, Zoonotic and Arthropod-borne Pathogens, Virginia Polytechnic Institute and State University, Blacksburg, VA. e-mail: xjmeng@vt.edu.

Conflicts of interest
The authors disclose no conflicts.

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.01.005